I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: June 6, 2008 Signature: (William K. Merkel)

Docket No.: 27373/33638A (PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Weichselbaum et al.

Application No.: 09/964,042 Confirmation No.: 1056

Filed: September 26, 2001 Art Unit: 1635

For: Treatment of Tumors with Genetically Engineered Herpes Virus Examiner: J. E. Angell

DECLARATION UNDER 37 C.F.R. § 1.132

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. I, Bernard Roizman, Sc.D., declare that:

2. I am a named co-inventor, along with Ralph Weichselbaum and Richard Whitley, on the above-identified patent application. I am familiar with the contents of the patent application and make this declaration to provide information that may be relevant to examination of the application. A copy of my *curriculum vitae* is attached as Exhibit A.

3. I am aware that the Examiner of the above-identified patent application is maintaining that Advani et al., Int. J. of Radiation Oncology Biology Physics vol. 39(2), Supplement 1, 251 (1997) (i.e., the Advani abstract, a true copy of which is attached as Exhibit B), a reference of record, discloses the administration of herpes simplex virus R7020 to mice bearing human tumor xenografts resulting in tumor reduction. I am further aware that the Examiner has taken the position that Carroll, Ann. Surg. 224:323-330 (1996) (i.e., Carroll, a true copy of which is attached as Exhibit C), another reference of record, discloses the use of herpes simplex virus hrR3, an attenuated HSV, to treat colon carcinoma cells that have metastasized to the liver, and asserts that Carroll's use of the attenuated HSV hrR3 to treat a non-CNS tumor provides a reason to adapt the Advani method of treating CNS tumors using HSV R7020 to the treatment of non-CNS tumors, thereby arriving at the subject matter of the pending claims.

4. I am a co-author of the Advani abstract, which summarizes an experiment to measure the level of replication of two herpesviruses, i.e., HSV R3616 and HSV R7020. The Advani abstract discloses that a single quantity of virus (2×10^7 pfu) was administered to mice bearing human glioma tumor xenografts. At specified time intervals, tumors were removed, homogenized, and viral titers were determined using conventional techniques and permissive Vero cells. For tumors exposed to HSV R3616, those time intervals were days 3, 5, 7 and 14 post-infection; for HSV R7020, those time intervals were days 3, 5 and 7, but not day 14. The results of determining the viral titers revealed that the concentration of HSV R7020 had dropped to about zero by day 7 and, hence, there was no scientific purpose served by determining viral titers of HSV R7020 beyond this point in time.

5. In the specification of the above-referenced application, Example 1 reveals that an SQ-20b tumor xenograft exposed to HSV R7020 "began to regress 13 days after infection . . . ." Specification, page 8, lines 11-13. There is no evidence in the materials I have reviewed that would indicate to one of ordinary skill in the art that HSV R7020 would reduce a glioma tumor mass and, in view of the disclosure in the above-captioned specification that HSV R7020 did not begin to reduce an SQ-20b tumor until 13 days post-infection, there would not have been a reasonable scientific basis for inferring tumor mass reduction from the seven-day replication study of HSV R7020 reported in the Advani abstract.

6. Consistent with the foregoing observations, the Advani abstract does not disclose or suggest that HSV R7020 administration to a mouse bearing a human glioma xenograft resulted in reduction of that tumor or any other tumor. The single HSV R7020 experiment described in the Advani abstract was stopped at 7 days post-infection and the only evidence of record relating to HSV R7020-induced tumor mass reduction is the 13 days post-infection required to begin to see SQ-20b tumor mass reduction, as described in the above-captioned application and not in the art of record.

7. One of ordinary skill in the art relevant to the pending claims would have a fundamental understanding of oncology and would understand, at a minimum, the basic scientific principles underlying viral oncology. Those principles include a positive correlation between the amount of an oncolytic virus administered to tumor cells and the level of destruction of those tumor cells, the positive, and typically rapid, growth rate of tumor cells, the negative correlation between the amount of an oncolytic virus administered and the safety of such administration to the host organism, and that effective treatment may

involve tumor stasis (i.e., neither tumor progression nor regression) or tumor regression (e.g., a reduction of tumor mass). *See* U.S. Patent No. 5,342,947, col. 14, lines 19-23, attached as Exhibit D, for disclosure relating to tumor stasis.

8. One of ordinary skill in the art, aware of the principles noted in paragraph 7, would understand that a therapeutically effective dose of a particular oncolytic virus is dependent on the virulence of that virus towards tumor cells, the rate of growth of the tumor cells in the host organism being treated, and the virulence of that virus towards healthy cells of the host organism.

9. The Advani abstract does not disclose the dose-response relationship of HSV R7020 administered to glioma tumor cells in mice. The Advani abstract is also silent on the rate of gliomal tumor cell growth in mice, although it was known in the art that glioma tumors grow rapidly, due at least in part to the greater proportion of cells actively growing than is found in healthy tissues. *See* Schold et al., J. Neuro-Oncology 1:5-14 (1983) attached as Exhibit E. The Advani abstract also lacked any disclosure relating to the safety of HSV R7020, other than noting that this attenuated virus was less attenuated than HSV R3616, and thus more virulent than HSV R3616 but less virulent than wild-type HSV. Notably, no healthy mouse tissue was examined in the study reported in the Advani abstract.

10. As established in the preceding paragraphs, the Advani abstract did not expressly disclose that HSV R7020 administration resulted in a reduction in glioma tumor mass. In addition, the Advani abstract did not implicitly or inherently make such a disclosure because neither the abstract nor the knowledge in the art established that one of ordinary skill in the art would recognize that administration of 2×10^7 pfu HSV R7020 would produce a rate of glioma cell killing that exceeded the rate of glioma cell growth for xenografts in mice having an open-ended size of ">200 mm^3," which would be understood to mean greater than 200 mm^3.

11. Further, a reference in the Advani abstract to "treatment" did not distinguish between treatment resulting in tumor stasis versus treatment resulting in tumor regression. Only the latter form of treatment would result in a reduction of tumor mass.

12. For the foregoing reasons, the Advani abstract does not provide a reasonable basis for one of ordinary skill in the art to believe that any amount of HSV R7020 would be sufficiently effective to kill tumor cells at a rate that exceeded the rate of tumor growth, thereby resulting in a reduction of tumor mass.

13. With respect to the issue of safety, the Advani abstract summarized an experimental determination of a time series of viral titers in homogenized mouse xenografts. The reference does not disclose an analysis of any tissue other than the cancerous xenograft. Accordingly, the Advani abstract was completely silent on any possible effect of HSV R7020 on any healthy tissue, and thus was completely silent on the issue of the safety of this HSV.

14. For reasons elaborated in the preceding paragraphs, one of ordinary skill in the art would not have understood that HSV R7020, or any other HSV modified in conformity with the claims pending in the above-captioned patent application, would be safe to administer to a patient based on a review of any of the art being cited against the pending claims, including the Advani abstract. Accordingly, one of ordinary skill in the art did not know, and would not have developed an expectation, that there would be any amount of HSV R7020 that would be a therapeutically effective amount because there was no disclosure or suggestion that HSV R7020 would be sufficiently safe to use as a therapeutic.

15. For the reasons provided herein, the Advani abstract does not provide a reasonable basis for one of ordinary skill in the art to believe that any amount of HSV R7020 would be sufficiently safe to administer to a patient.

16. I am further aware that the Examiner has cited Carroll as disclosing an attenuated HSV being used to treat a non-CNS tumor, thereby providing motivation to modify Advani's method to arrive at a method of using HSV R7020 to treat non-CNS tumors. One of ordinary skill in the art would not have been motivated to modify Advani's method based on the disclosure of a non-CNS tumor being exposed to attenuated HSV hrR3 because the mechanism by which HSV hrR3 is attenuated is different from the mechanism by which HSV R7020 is attenuated.

17. HSV R7020 is a multi-mutated HSV having a deletion of one inverted repeat and the genes located therein. More particularly, HSV R7020 is deleted for the U_L24, U_L55 and U_L56 genes, is deleted for one of two copies of each of genes $\alpha 0$, $\gamma_1 34.5$, ORF O, and ORF P, contains a heterologous U_L23 gene, and contains HSV-2 genes encoding glycoproteins G, D, I and part of E. The HSV hrR3 disclosed in Carroll is an HSV deleted for U_L39 encoding the large subunit of ribonucleotide reductase (ICP6).

18. HSV R7020 is attenuated relative to wild-type HSV. That attenuation is due to the absence of inverted repeats within the HSV R7020 genome, augmented by the absence of U_L23m, U_L55, and U_L56.

19. HSV hrR3, in contrast to HSV R7020, retains the inverted repeat structure of the wild-type HSV genome. HSV hrR3 is attenuated relative to wild-type HSV because the deletion of U_L39 in HSV hrR3, leading to a failure to express the large subunit of ribonucleotide reductase, renders the virus deficient in synthesizing the nucleotide building blocks it needs for viral replication. Host nucleotides may be available in a given cell, however, and the deletion of U_L39 does not interfere with the ability of the virus to use host nucleotides in replication. The reduced availability of nucleotide building blocks impedes, but does not prevent, successful infection.

20. HSV hrR3 is attenuated through a mechanism completely different from the mechanism or mechanisms responsible for attenuation of HSV R7020. The fact that each of these viruses is less virulent than wild-type HSV (i.e., each is attenuated) does not mean that these two viruses are interchangeable.

21. One of ordinary skill in the art would not be motivated to modify Carroll's method by substituting HSV R7020 for HSV hrR3 because the mechanisms of attenuation of these two viruses differ. One of ordinary skill would understand that a demonstration that an HSV (e.g., HSV hrR3) with a particular form of attenuation could successfully destroy tumor cells without an unacceptable destruction of healthy cells would not be relevant to whether a different HSV (e.g., HSV R7020), with a different form of attenuation, could be successfully used in analogous methods.

22. For the foregoing reasons, one of ordinary skill in the art would not look to guidance from Carroll in modifying any method disclosed in the Advani abstract because Carroll's HSV hrR3 is attenuated by a mechanism completely unrelated to the mechanism(s) by which Advani's HSV R7020 is attenuated.

23. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

May 7 2008
Date

Bernard Roizman